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Evaluation and Management of Patients with Inhalation Injury

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Inhalation injury, present in approximately one third of burned patients treated at burn centers, increases mortality by a maximum of 20% in relation to age and extent of burn. The development of animal models of inhalation injury has made possible the identification of both the airway and vascular responses evoked by smoke inhalation. Inflammatory occlusion of terminal bronchioles and necrosis of the endobronchial mucosa render the airway and pulmonary parenchyma susceptible to infection and the resulting pneumonitis further increases mortality. Early diagnosis, best achieved by endoscopic bronchoscopy and ¹³³xenon ventilation perfusion scan, permits timely application of high-frequency ventilation that appears to reduce the incidence of pneumonia and to decrease mortality. Pharmacologic agents give promise of ameliorating the deleterious changes of the vasculature. The recent advances in understanding inhalation injury have identified the research needed to further improve patient salvage.

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The incidence of inhalation injury increases from less than 10% in patients with a mean burn size of 5% of the total body surface to more than 80% in patients with a mean burn size of 85% or more of the total body surface and is present in approximately one third of patients treated at burn centers. The inflammatory tracheobronchitis that occurs as a consequence of the inhalation of smoke and other irritative products of incomplete combustion increases the mortality of burned patients in relation to both age and extent of burn by a maximum of 20%. Slough of the necrotic damaged airway mucosa denudes the underlying tissue and renders it susceptible to microbial tracheobronchitis. The subsequent development of bronchopneumonia represents the aggregate effect of early atelectasis consequent to occlusion of the small airways due to inflammatory edema, and distal spread of the microbial tracheobronchitis. The frequent occurrence of respiratory insufficiency and the high incidence of bronchopneumonia (38% of 373 patients treated during a 5-year period) as well as the early onset of that pneumonia in patients with inhalation injury (69% occur within the first week postinjury) emphasize the importance of early accurate diagnosis (1).

PATIENT EVALUATION

A predictor of inhalation injury (Y) based on the readily available clinical variables of injury in a closed space (CLSP), presence of facial burns (FB), total extent of body surface burned (TBS), and age (A) has been

derived by a stepwise logistic regression. Prediction of the presence of inhalation injury, using the formula $Y = -4.4165 + 1.61 (CLSP) + 1.77 (FB) + 0.0237 (TBS) + 0.0268 (A)$, closely approximated the observed incidence of inhalation injury in 1,058 consecutive burned patients treated at the U.S. Army Institute of Surgical Research during the years 1980-1984 (1). Although the formula recognizes the fact that being burned in a closed space generally correlates with the presence of inhalation injury and that most patients with inhalation injury have face burns, certain patients burned in a closed space and most patients with face burns do not have inhalation injury. Other clinical signs, such as cough, hoarse voice, bronchorrhoea, dyspnea, and wheezing, are often delayed onset (2). Conversely, the presence of carbonaceous material in the airway secretions, generally a reliable indication of inhalation injury, may not be evident at the time of patient admission to a burn center as a result of rapid clearance of such secretions.

Chest roentgenograms are profoundly insensitive in detecting even severe inhalation injury in the early post-injury period. Clark et al. considered chest roentgenograms taken on the day of injury to be falsely negative in 92% of 106 patients with inhalation injury (3).

The insensitivity of chest roentgenograms and the unreliability of the clinical signs of inhalation injury necessitate use of other diagnostic techniques. The most easily performed reliable diagnostic modality is fiberoptic bronchoscopic examination of both the supra- and infraglottic airway to identify inflammatory changes and damage of the airway mucosa (Fig. 1). Impairment of the bronchial circulation in an inadequately resuscitated burned patient may prevent the development of inflam-

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FIG. 1. Endoscopic view showing dark foci of carbon deposition (at 12 and 7 o'clock) and inflammation of the bronchial mucosa, at left lower margin of field, in a patient with smoke inhalation injury.

matory changes in the airway mucosa and result in a falsely negative endoscopic examination (4). Conversely, chronic bronchitis, present in a heavy smoker, may result in a falsely positive endoscopic examination.

Bronchoscopic examination may also fail to detect injury caused by the inhalation of a finely particulate aerosol since the site of airway deposition of particles with a mass median diameter of less than 0.05 microns is principally in the terminal bronchioles and pulmonary parenchyma (5). For that reason, a ^{133}Xe ventilation perfusion scan should be performed in any patient suspected of having an inhalation injury in whom the bronchoscopic examination has been negative. Unequal lung field radiation density and/or retention of the radiolabelled gas in the lung field beyond 90 seconds following peripheral vein injection of 10 microcuries of radiolabelled xenon constitute a positive scan (6). Postburn hyperventilation, which may develop following resuscitation, may produce a falsely negative scan if the scan is performed beyond the first 48 hours postburn. Conversely, chronic bronchitis can produce a falsely positive lung scan.

Several pulmonary function tests ranging in sophistication from the simple measurement of arterial oxygen tension to measurement of the maximum expiratory flow volume loop have been correlated with the presence of inhalation injury, but the equipment necessary to perform the more sophisticated tests and the essentiality of full cooperation by the patient limit their usefulness (7). The use of fiberoptic endoscopic examination of the airway in combination with the ^{133}Xe ventilation perfusion lung scan diagnoses the presence of inhalation injury with 93% accuracy (8) (Table I).

PATIENT MANAGEMENT

The treatment of inhalation injury is guided by the severity of the resulting pulmonary insufficiency. In patients with minimal disease, the administration of warm,

TABLE I
Diagnosis of inhalation injury

Diagnostic Modality	Diagnostic Accuracy
Pulmonary function tests	91%
^{133}Xe lung scan	87%
Fiberoptic bronchoscopy	86%
^{133}Xe lung scan plus bronchoscopy	93%

humidified oxygen may be the only treatment needed. In patients with more severe airway injury, frequent suctioning may be necessary to remove secretions and debris. Cylindrical casts of the airway composed of necrotic endobronchial mucosa, inspissated exudate, and inflammatory cells may cause acute obstruction of the airway, necessitating emergency bronchoscopy using a rigid bronchoscope to extract the occluding debris.

AIRWAY INJURY

The development of an animal model of inhalation injury, in which mortality and changes in pulmonary function are proportional to the dose of smoke, has permitted studies of both the morphologic and functional changes of the lung caused by such injury (9, 10) (Fig. 2). Of particular interest have been studies in the ovine model of inhalation injury documenting dose-related changes in the matching of ventilation and perfusion in the lung. Within 24 hours after a moderate inhalation injury, the normally well matched ventilation and perfusion of the lung are significantly altered by the appearance of a poorly ventilated compartment (V_a/Q ratio less than 0.1) in association with a modest elevation of true shunt (11). This change is entirely consistent with acute inflammatory occlusion of the small airways of lung tissue in which blood flow is maintained. Such occlusion explains at least in part the atelectasis that occurs in patients with inhalation injury. The administration of 100% oxygen to the study animals obliterated the low air flow compartment but that effect was accompanied by a twofold increase in true shunt, a change consistent with alveolar collapse in the involved segments (12).

The apparent importance of small airway occlusion and alveolar collapse in the development of the complications of inhalation injury makes the maintenance of ventilation and prevention of atelectasis a primary clinical concern. In patients with mild injury, incentive spirometry may be sufficient, while patients with more severe injury may require endotracheal intubation and mechanical ventilation. The ability of high-frequency ventilation to provide adequate oxygenation at a lower FIO_2 , adequate ventilation at lower peak and mean airway pressures, and increase the clearance of endobronchial secretions has prompted an ongoing clinical trial of the prophylactic use of interrupted-flow high-frequency positive pressure ventilation for patients with inhalation



FIG. 2. A) Gross specimen of trachea and lungs from an ovine model of inhalation injury. The dark mottling of the lung surface is caused by fine carbon particles in the lung parenchyma. Note, at end of pointer, the intratracheal cast formed by cellular debris. The trachea underlying the pointer has been denuded of mucosa. B) Photomicrograph of an ovine tracheal wall following inhalation injury showing focal loss of mucosa/epithelium in right half of field and intraluminal membrane composed of inflammatory cells, necrotic mucosal cells, and serum lining the tracheal wall.

injury (13). The ventilator used in that study has a sliding Venturi that provides a high-frequency pulse and entrains humidified bias gas. Subtidal breaths, the inspiratory/respiratory ratio of which can be varied, are provided at a frequency of up to 600 per minute. Periodically, the ventilation cycle is interrupted to return the airway pressure to baseline. The subtidal/baseline ratio can be adjusted to manipulate arterial oxygen and carbon dioxide tension.

Inhalation injury has been documented in the trial patients by $^{133}\text{xenon}$ ventilation-perfusion lung scan or bronchoscopic examination. The need for intubation and mechanical ventilation of the study patients has been defined by the usual criteria, i.e., a respiratory rate of greater than 30 per minute, an arterial oxygen tension of less than 60 torr on an FIO_2 of greater than 0.4, a minute ventilation of greater than 20 liters, an arterial PCO_2 of more than 45 torr, or severe laryngeal edema. Nine of the first 37 patients studied have expired, a significant decrease from the mortality anticipated by the currently used mortality predictor at the U.S. Army Institute of Surgical Research. Concurrently, the occurrence of pneumonia has been significantly reduced. Complications related to use of the high-frequency ventilator

have included: two cases of extensive subcutaneous emphysema, two cases of necrotizing tracheobronchitis attributable to inhalation injury per se, desiccation, local increase in airway pressure, or some combination thereof; and three cases of deep venous thrombosis. These complications have prompted a current project to develop an effective oscillating ventilator for use in adult burned patients with inhalation injury.

A small subset of patients with inhalation injury will manifest bronchospasm of some degree. In general, such bronchospasm is best treated by the administration of an aerosolized bronchodilator such as isuprel or albuterol or systemic administration of aminophylline (7). The use of steroids for other than severe intractable bronchospasm, as in a severe asthmatic, is contraindicated since several studies have shown that the prophylactic use of steroids was either ineffectual or associated with an increased incidence of infectious complications (14-16). Similarly, the prophylactic use of aerosolized antibiotics for pneumonia prophylaxis in patients with inhalation injury remains of unverified effectiveness. A study of aerosolized gentamicin prophylaxis in patients with inhalation injury demonstrated no effect of such treatment on occurrence of roentgenographic infiltrates, need for

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FIG. 2B.

TABLE II
Effect of platelet activating factor antagonist (CV-3988) on pulmonary function following smoke inhalation

Treatment Groups	Dynamic Resistance	Static Compliance
Smoke only	32.0	92.8
Smoke plus CV-3988		
Pre- and post-smoke treatment	19.7	174.3
Post-smoke treatment only	17.1	195.3

mechanical ventilation, incidence of sepsis, or mortality. In that study even the recovery of *Pseudomonas* organisms from the endobronchial secretions was insensitive to the gentamicin aerosol (14).

Studies by others have either implicated or exonerated other pathogenetic factors in the pulmonary response to inhalation injury. Nieman et al. identified significant surfactant reduction following smoke inhalation in a canine model as indexed by an increase in minimum surface tension, a change that may contribute to the atelectatic sequelae of inhalation injury (17). Conversely, Prien et al. have reported that phosphatidylcholine composition of lung surfactant is normal 24 hours after inhalation injury (18).

VASCULAR INJURY

Direct injury to the vascular side of the alveolocapillary membrane as well as damage caused by oxygen radicals

and proteolytic enzymes produced by either activated leukocytes and/or humoral mediators, such as prostanooids and leukotrienes, may also contribute to the sequelae of inhalation injury. Nieman et al. have reported that the inhalation of wood smoke in a canine model is associated with a moderate increase in pulmonary vascular permeability (19). The studies of Hales et al. demonstrating the importance of the bronchial artery in the genesis of pulmonary edema following smoke injury in a canine model provide further support of the importance of vascular injury in the pathogenesis of inhalation injury (20).

The importance of activation of the formed elements of the blood in the pathophysiologic response to smoke inhalation has been assessed in yet other studies. Basadre et al., using an ovine model of cotton smoke inhalation injury, demonstrated that the production of oxygen radicals and antiprotease consumption following the injury could be attenuated by preinjury induction of leukopenia (21). Those authors concluded that circulating leukocytes and the release of their cytotoxic metabolites contributed to the lung injury caused by smoke inhalation. In other studies by that same group, the administration of the cyclooxygenase inhibitor ibuprofen was found to reduce the lung lymph flow in animals with inhalation injury (22). Studies by Prien et al. have demonstrated no increase in lung weight of the uninjured lung following

insufflation of the other lung with smoke (23). The latter studies have been interpreted as impugning the importance of hematogenously mediated pulmonary injury following smoke inhalation. Huang and colleagues, using a caprine model, identified a significant increase in arterial thromboxane A_2 concentration within 5 minutes of the injury in association with a progressive decrease in peripheral platelet counts, changes that they considered indicative of platelet aggregation within the pulmonary microvasculature that were temporally related to an increase in extravascular lung water (24).

Recent studies, in the authors' laboratory, have implicated yet another cytokine, platelet activating factor, in the alterations of pulmonary function that occur following inhalation injury. Platelet activating factor promotes platelet aggregation, produces vasodilatation, and increases vascular permeability. This cytokine also induces bronchospasm and causes neutrophil aggregation and degranulation with release of lysosomal enzymes. Using the previously described ovine model of moderate inhalation injury, Ikeuchi et al. found that pre- and postinjury administration as well as postinjury administration alone of the platelet activating factor antagonist CV3988 maintained arterial PO_2 and arterial PCO_2 at levels higher and lower, respectively, than in untreated animals (25). The animals treated with the PAF antagonist also had significantly lower dynamic resistance and significantly higher static compliance compared to untreated control animals (Table II). In the antagonist-treated animals blood flow to the low V_a/Q compartment and to true shunt were both significantly decreased. Last, examination of pulmonary tissue obtained at autopsy in the PAF antagonist-treated animals showed marked decrease in atelectasis, vascular congestion, and intrapulmonary polymorphonuclear leukocyte accumulation.

RESEARCH ADVANCES AND NEEDS

Clinical and laboratory investigations, sponsored by both the U.S. Army Medical Research and Development Command and the National Institute of General Medical Sciences, have significantly advanced our understanding of inhalation injury during the past decade. Identification of the mortality enhancing effect of inhalation injury has emphasized its importance as a clinical problem and prompted the development of reliable methods of diagnosis as well as the development of several animal models of the disease. Clinical studies have identified the need for increased volumes of resuscitation fluid in patients with inhalation injury and the resulting modifications of fluid therapy have decreased the incidence of early post-injury organ failure (26). Laboratory studies utilizing the animal models have identified the significance of airway injury and prompted current trials of high-frequency ventilation that give promise of decreasing both mortality and the pneumonitic sequelae of inhalation injury. Recent studies have implicated products of cell injury

and activation in the pathophysiologic response of the lung to smoke inhalation.

Persistent clinical problems, as well as those revealed by the recent advances in the understanding of inhalation injury, define the areas where future research is most needed. Since current diagnostic modalities simply indicate whether inhalation injury is present and do not measure severity of injury, a technique by which the severity of inhalation injury and volume of lung tissue involved can be quantified is critically needed to improve patient stratification in clinical trials. The importance of atelectasis in the pathogenesis of the response to inhalation injury and the changing epidemiology of the pneumonitic sequelae speak for prophylactic trials of synthetic surfactant and broad-spectrum antibiotics. Accumulating evidence that activated cells and cytokines influence the response to inhalation injury speaks for a need to evaluate cytokine inhibitors and oxygen radical scavengers. The development of a standard animal model of inhalation injury in which anatomic and functional changes reliably mimic those in man will eliminate species-specific differences in laboratory studies of pathogenesis and treatment. Last, although the prophylactic use of high-frequency ventilation in patients with inhalation injury appears promising, the limitations of available devices speak for the development of improved mechanical ventilators. Meeting these research needs by technological solutions to the problems of diagnosis and ventilatory support, development of improved means of infection prevention and control, and identification of effective pharmacologic regimens to modify the airway and vascular responses will further reduce the morbidity and mortality associated with inhalation injury, the single most important co-morbid factor in severely burned patients today.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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DISCUSSION OF SECTION ON PULMONARY INJURY

DR. MYERS: Stuart Myers from Houston. I have a theoretical question for Doctor Maier. Based on some of the data that Doctor Pruitt showed with his inhibitor of PAF, one of the questions I had was, since PAF has to be released, at least arachidonic acid needs to be released with the deacylation step, at least what I have been told before is that the reacylation step is actually more active than the deacylation.

So, the question I have is if you block the utilization of

arachidonic acid with a cyclooxygenase/lipoxygenase inhibitor would that drive the arachidonic acid back into the phospholipid and could that theoretically then inhibit the release of PAF? If that is possibly true, could that explain some of the survival studies with cyclooxygenase or eicosanoid inhibition described for different shock states?

DR. MAIER: The quick answer is, yes, I think theoretically that is quite possible because, as you say, the breakdown of PAF is more efficient than the formation. Once it is formed, the deacylation with addition of arachidonic acid back to the C-2 carbon is very efficient. In fact, 80 to 90% of the breakdown of PAF ends up with arachidonic acid as the lyso-PAF. I think you are right that if you shut down cyclooxygenase so the arachidonate is available for that process, that it probably does help down regulate the system.

The problem with that theory though is that if you look at the stimulated cell from inflammatory stimuli, it also up regulates protein kinase C. And protein kinase C phosphorylates the deacetylation process and down regulates it so therefore it prolongs the activity of the PAF and its survival. So, the theory is good. I can't tell you where the net balance would come out in vivo in an inflammatory state.

DR. DUNN: I also had a question for Doctor Maier. Basically, I was very intrigued by the data that you showed indicating that some of the less toxic endotoxins, in fact, act as inhibitors for macrophage monokine release. I have been scratching my head, as it were, over some of our data that we have generated within the last month or so looking at FC-binding of radiolabeled endotoxin. In fact, we have come to somewhat the same conclusion, that lipid A and lipid X can competitively inhibit this process, but have not really extended it yet to looking at monokine activation.

What I was specifically wondering was, when we have used both IgG and IgM monoclonal antibodies to block this process, we have gotten very disparate results. It would appear that there was some indication that the FC receptor for certain antibodies may enhance binding of certain types of endotoxin as well as lipid A and that others that don't possess that such as IgM won't do that.

Do you think that there is some common pathway here where there is one receptor that you are looking at or, in fact, do you think that there are two receptors? Because with the data that you showed in conjunction with what I just mentioned, I really wonder if there are two different receptors that are acting on different parts of the endotoxin molecules. That may explain some of the disparate results that I think many of us in the room may have seen in looking at this in vitro.

DR. MAIER: I think there are at least two different receptors. I guess you can be either in the camp that there is a putative endotoxin receptor or there is not. I personally don't think there is one but a lot of people believe that there is. Actually, my own data with competitive inhibition actually look like it is competing for a specific membrane receptor and would actually support that there is one.

Doctor Ulevitch, on Saturday, I am sure in his discussion will present the binding to the lipopolysaccharide binding protein which is the acute phase protein that is seen after all stress states. Actually, the studies that he has done very nicely show that, as I showed you, as you change the lipid A portion of endotoxin, not only do you not lose the ability to stimulate the macrophage but you also do not lose the ability to bind to the lipopolysaccharide binding protein. Doctor Ulevitch has shown very nicely that there is a receptor for the LPS complex and then that interaction probably dissociates and the endotoxin enters the cell and causes stimulation.

What binding to the protein does is to allow the cell to recognize that even more efficiently and to get the endotoxin to the membrane surface so it can interact with either a second

receptor or be internalized by the cell and cause cell stimulation. I think what you just presented is that the FC receptor probably can function in a similar fashion in presenting the endotoxin molecule to either the receptor or to just the cell membrane per se and as a lipid it interdigitates more efficiently once it gets to the surface.

DR. TRABER: I wanted to address my question to Doctor Pruitt, although I have many questions for all of the other panelists. But, Doctor Pruitt, I was very interested in your comments relating to ciliated epithelial cells because we have done a similar study dose response-wise. If we look at a specific area of the airway, there doesn't appear to be a dose response relationship. Once the cells fall off, they fall off, and whether you go higher or not, the number of cells that fall off appears to be the same. However, we see that the lesion seems to grow downward in the airway. I was wondering whether you saw a similar phenomenon.

I would also like to address one point that you made in your final discussion, that was the sheep not being a good model for using ventilators because we have trained two generations of anesthesia residents using sheep and the ventilator. I had discussed this with one of your associates who did the ventilator study. We don't use depolarizing blocking agents on the sheep. They have a tendency to do very poorly with that but as we reported in 1984, we just used the ventilator alone and we find that they are very good for training residents to use ventilators, or very good models for studying ventilators.

DR. PRUITT: I think it makes good sense if you are training veterinarian anesthesiologists to use sheep. I think that the severity of the injury that I referred to was as you describe it, Doctor Traber. It is a more extensive area involvement rather than severity of injury to individual cells.

DR. TRABER: Of course, we were not training veterinarian anesthesiologists, Doctor Pruitt. We were training regular anesthesiologists. It was a great disappointment to the ECMO people when they first came to Galveston because they couldn't get very many pediatric patients for the ECMO studies because our anesthesiologists were so efficient at applying the ventilator to them.

DR. HERNDON: Of course, I also learned not to use ventilators in our laboratory.

DR. MOLDAWER: Lyle Moldawer at Cornell. I was very much impressed with the two-hit hypothesis. My only concern is your tendency to give the credit to the neutrophil, or Doctor Harken's to give it to the neutrophil and you to give it to the macrophage. Aren't the data equally consistent with the first hit being an endothelium phenomenon and predominantly that the changes that . . . well, first of all that the endothelium responds to endotoxin by producing these mediators, interleukin-1, interleukin-6. Then, they go on to produce IL-8. It is this combination of cytokines which can explain the up regulation and subsequent down regulation of the adhesion molecules.

DR. HERNDON: I think we'd better ask Doctor Demling whether it is the endothelial cell. You get prejudice from Doctor Maier.

DR. MAIER: Actually, I was going to volunteer, Bob. I was just going to say that I think you shouldn't look at it as a step function as it is a first step which is priming or whatever and then you get the second step which is overt disease. It is a very slow continuum in a very large gray area. I think, in regards to Bob's comment, what he was saying about the xanthine oxidase

and the endothelial cell producing just enough oxygen to stimulate the endothelial cell to produce PAF to produce IL-8, then recruits the neutrophil, activates the neutrophil, it depends on how extensively that process continues as to whether it is a physiologic recruitment and no injury is produced by the neutrophils or pathologic recruitment, where you get massive invasion of neutrophils and a significant tissue destruction.

DR. DEMLING: I think it would be hard to attribute the initial response to an endothelial cell and not have the endothelial cell leak if it is the same cytokines that are released the second time because you don't have to attribute an increase in permeability which is characteristic of the second time due to cytokine and PAF release and not an increase in permeability the first time as a result of a similar release. Now, Doctor Ward will describe a number of agents, particularly xanthine oxidase, being activated by the neutrophils initially as a potential mechanism for the later hit phenomenon. But, even that doesn't make a lot of sense because if you think of the endothelial cell as loaded with xanthine oxidase, it would sort of autodestruct initially.

DR. MOLDAWER: But, isn't it a graded phenomenon so that at a low hit, a soft hit, one can get up regulation of these adhesion molecules and production of these cytokines without having changes in the architecture of the endothelium?

DR. DEMLING: That would work if the initial response was very minor. But you know, a massive, massive burn is a huge inflammatory response. Yet, as Frank showed, the lung is very protected from that initial release. That compared to the second release, which needs to be very minor, even transient bacteremia, you would think that if the endothelial cell was the initial organ hit, it would respond with a 100% burn, a 90% burn, and it doesn't. It doesn't seem to be affected at least in the lung.

DR. MOLDAWER: Thank you.

DR. JEEVANANDAM: Jeevanandam from Phoenix, Arizona. I would like to add the seventh field of research in inhalation injury of Doctor Pruitt. A group of compounds called polyamines, putrescine, spermidine, and spermine are pyrimidines and they are involved in the protein metabolism. We have reported, in acute trauma patients, the increased involvement of these polyamines in injury. Now, I would like to ask all the distinguished panel to enlighten us if there is any polyamine research done on the lung injury with the ARDS or inhalation or burn injury?

DR. PRUITT: I understand that your question is, is anyone studying the role of pyrimidines.

DR. JEEVANANDAM: Polyamines.

DR. PRUITT: Polyamines. Putrescine and spermine.

DR. JEEVANANDAM: Spermine and spermidine.

DR. PRUITT: Yes. Not that I am aware of. That has been an interest of Doctor Moody's group over in Houston but it has been related to oncologic processes, I believe. I am not aware of anything about polyamines. How about trauma patients, Doctor Maier?

DR. JEEVANANDAM: The reason why I ask the question is that the polyamines are organic cations. Their levels are increased in stress conditions. Now, perhaps in the lung injury also, if the parenchymal cells are more effective in protein metabolism, perhaps the study of them may shed some light and treatment of them by some nasal spray or something like that.

DR. HERNDON: It is an interesting observation.

DR. PRUITT: They are not called putrescine for nothing. You would surely hate to have nasal sprays made out of putrescine.